Asymmetric 1,4-Additions to γ-Menthyloxybutenolides. (part IV) Two Enantioselective Syntheses of 2-Methyl-1,4-butanediol.

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Published in:
Synthetic Communications

DOI:
10.1080/00397919208019320

SYNTHETIC COMMUNICATIONS, 22(9), 1367-1376 (1992)

ASYMMETRIC 1,4-ADDITIONS TO γ-MENTHYLOXYBUTENOLIDES;(part IV[1]) TWO ENANTIOSELECTIVE SYNTHESES OF 2-METHYL-1,4-BUTANEDIOL.

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Abstract: Based on the asymmetric Michael addition to 5(R)- and 5(S)-menthyloxy-2[5H]-furanone two new syntheses of enantiomerically pure R- and S-2-methyl-1,4-butanediol are described.

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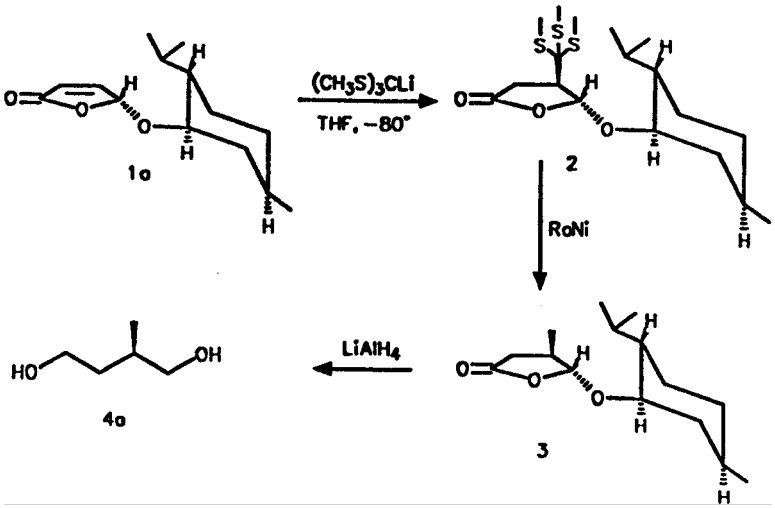
Chiral γ-butyrolactones are important building blocks in the enantioselective synthesis of acyclic compounds with arrays of methyl- and hydroxy-substituents at vicinal or remote stereogenic centers[2]. For instance Hannessian and co-workers reported the use of (S)-4-hydroxymethyl-butyrolactone in the synthesis of amphotericin B segments[3]. In our group reactions with enantiomerically pure 5(R)-(l-menthyloxy)- (**1a**) and 5(S)-(d-menthyloxy)-2[5H]-furanone (**1b**) are investigated, due to the excellent stereocontrol exerted by the γ-menthyloxy substituent, the easy way of preparation of these synthons in enantiomerically pure form and the use of cheap d- or l-menthol as chiral auxiliary[4].

In this paper we wish to present two enantioselective syntheses of R- (**4a**) and S-2-methyl-1,4-butanediol (**4b**).

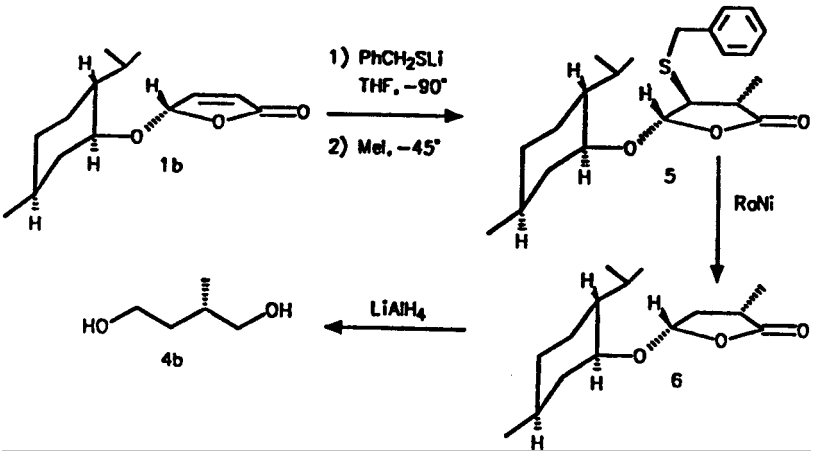
scheme 1



The first synthesis is based on the stereoselective Michael addition of lithiated trismethylthiomethane to 5(R)-(l-menthyloxy)-2[5H]-furanone (**1a**). This Michael addition is a facile process at -80°C and after quenching with a saturated ammoniumchloride solution lactone **2** was obtained in 84% yield.

On the basis of ^{1}H-NMR (J_{H4-H5} = 0Hz) it is demonstrated that the trans adduct is formed. After Raney Nickel reduction of **2** lactone **3** was obtained in 90% yield. Subsequent reduction of **3** using $LiAlH_4$ in THF provided **4a** quantitatively ($[\alpha]_D^{20}$ 13.6, c 3.3 MeOH). The chiral auxiliary l-menthol was recovered in this step. Following this reaction sequence enantiomerically pure (R)-2-methyl-1,4-butanediol (**4a**) was obtained in 76% overall yield from (**1a**).

scheme 2



In the second route 5(S)-(d-menthyloxy)-2[5H]-furanone (**1b**) was used in a tandem 1,4-addition lactone-enolate methylation. The initial Michael addition of lithiated benzylmercaptan (THF, -90°C) to 5(S)-(d-menthyloxy)-2[5H]-furanone (**1b**) was followed by quenching with MeI (-45°C) of the resulting lactone enolate. The trisubstituted lactone (**5**) could be obtained quantitatively as a single isomer. The all trans configuration was present for C3, C4 and C5 as could be deduced from the ^{1}H-NMR spectra. A quantitative Raney Nickel reduction afforded 3(S)5(S)-3-methyl-5-(d-menthyloxy)-butyrolactone (**6**). Reduction of (**6**) with $LiAlH_4$ was performed in an identical way as described for compound (**3**). By this method enantiomerically pure (S)-2-methyl-1,4-butanediol (**4b**) was obtained in 80% overall yield from (**1b**). The enantiomeric excess was proven to be $\geq$98% by means of HPLC[4].

It should be noted that the addition of a lithiated mercaptan to **1** followed by a selective quenching reaction is not generally applicable for several reasons. When other lithiated thiols were applied as Michael donors, either no reaction occurred (with thiophenol) or the quenching reaction was unselective (using thio-ethanol or thio-t-butanol). Furthermore the quenching reaction of the lactone enolate, formed by the initial Michael addition of lithiated benzylmercaptane to (**1**), is only synthetically useful with MeI as alkylation agent, since with other halides very low yields were obtained (ethyliodide 5%, benzylbromide 9%, ethylbromide, i-propylbromide and n-butylbromide <3%).

In conclusion, new high yield, stereoselective routes to enantiomerically pure 2-methyl-1,4-butanediols have been developed.

experimental:

4(R)5(R)-4-(trismethylthiomethyl)-5-(l-menthyloxy)-butyrolactone 2: To a stirred solution of 1.54 g (10 mmol) trismethylthiomethane in 30 ml of THF under a N_2 atmosphere was added at -80°C 6.9 ml of n-Buli (1.5N in hexane, 10.4 mmol) followed by stirring for 0.5 h at this temperature. Subsequently 2.38 g (10 mmol) of 5(R)-(l-menthyloxy)-2[5H]-furanone **1a** in 10 ml of THF was added during 10 min to the white suspension, and the reaction mixture was stirred for 1.5 h at -80°C. Quenching of the reaction mixture with 200 ml saturated NH_4Cl was followed by extraction with ether (3x100ml), drying (Na_2SO_4) and evaporation of the solvent. Molecular distillation 190°C (0.06 mmHg) afforded 3.28 g (8.4mmol, 84%) of enantiomerically pure **2** as an oil. **IR**; neat, cm^{-1}: 1780 C=O **^{1}H-NMR**; $CDCl_3$ 300 MHz, δ (ppm): 5.88 (s, 1H) 3.52 (dt, 1H, J=4.0 Hz, J=10.6 Hz) 2.92-2.70 (m, 3H) 2.21-2.18 (m, 1H) 2.16 (s, 9H) 2.09-1.96 (m, 1H) 1.72-1.58 (m, 2H) 1.46-1.32 (m, 1H) 1.30-1.13 (m, 1H) 1.07 (m, 3H) 0.94 (d, 3H, J=6.5 Hz) 0.86 (d, 3H, J=7.0 Hz) 0.77 (d, 3H, J=7.0 Hz) **^{13}C-NMR**; $CDCl_3$ 75 MHz, δ (ppm): 175.39 (s) 101.19 (d) 76.98 (d) 71.00 (s) 51.20 (d) 47.59 (d) 39.44 (t) 34.13 (t) 31.17 (d) 31.02 (t) 25.25 (d) 22.87 (t) 22.10 (q) 20.73 (q) 15.39 (q) 13.53 (q) **HRMS**; M^+-CH_3S=392-47=345 calcd: 345.155, exp: 345.156; anal calcd for $C_{18}H_{32}O_3S_3$ C: 55.06%, H: 8.21%, exp C: 54.64%, H: 8.32%; $[\alpha]_D^{RT}$ -88.7 (c 1.8, $CHCl_3$)

4(R)5(R)-4-methyl-5-(l-menthyloxy)-butyrolactone 3: To a stirred solution of 80 mg (0.2 mmol) of **2** in 40 ml of THF were added 2 teaspoons of Raney-Nickel[5]. After stirring for 16 h the supernatant liquid was decanted from the solid material. Addition of 30 ml diethylether to the Raney-Nickel and stirring for 10 min was followed by decantation. This procedure was repeated thrice. The combined ethereal layers were washed with 10 ml water and dried (Na_2SO_4). After evaporation of the solvent 47 mg (0.18 mmol, 90%) of pure **3** was obtained as a white solid. mp 78.2-79.8°C, **IR**; KBr, cm^{-1}: 1780 C=O **^{1}H-NMR**; $CDCl_3$ 300 MHz, δ (ppm): 5.27 (d, 1H, J=2.2 Hz) 3.49 (dt, 1H, J=4.1 Hz, J=11.8 Hz) 2.82 (dd, 1H, J=8.2 Hz, J=17.6 Hz) 2.44-2.31 (m, 1H) 2.09 (dd, 1H, J=4.0 Hz, J=17.6 Hz) 2.10-2.00 (m, 2H) 1.70-1.58 (m, 2H) 1.46-1.15 (m, 2H) 1.11 (d, 3H, J=7.3 Hz) 1.07-0.76 (m, 3H) 0.93 (d, 3H, J=6.6 Hz) 0.87 (d, 3H, J=7.0 Hz) 0.77 (d, 3H, J=7.0 Hz) **^{13}C-NMR**; $CDCl_3$ 75 MHz, δ (ppm): 175.94 (s) 105.93 (d) 76.72 (d) 47.66 (d) 39.76 (t) 36.21 (d) 35.39 (t) 34.20 (t) 31.24 (d) 25.35 (d) 22.97 (t) 22.14 (q) 20.80 (q) 17.05 (q) 15.49 (q) **HRMS**; calcd: 254.188, exp: 254.187; anal calcd for $C_{15}H_{26}O_3$ C: 70.82%, H: 10.30%, exp C: 70.87%, H: 10.29%; $[\alpha]_D^{RT}$ -146.6 (c 0.9, $CHCl_3$)

(R)-2-methyl-1,4-butanediol 4a: To a stirred suspension of 0.21 g (5.6 mmol) $LiAlH_4$ in 50 ml THF at 0°C under a N_2 atmosphere was added a solution of 0.70 g (2.8 mmol) **3** in 10 ml of THF. The solution was stirred at 0°C for 30 min and subsequently at room temperature for 12 h. The

excess $LiAlH_4$ was destroyed by careful addition of 2 ml H_2O. The resulting mixture was filtered, the organic solvent was removed in vacuo, and 30 ml of water was added to the residue obtained. This mixture was washed with n-hexane (3x 50 ml) to remove the l-menthol. The water was evaporated under reduced pressure to afford 0.29 g (2.8 mmol, 100%) of the pure adduct as a colorless oil. Kugelrohr distillation (130°C, 15 mmHg) yielded 0.25 g (87%) of **4a**. **^{1}H-NMR**; $CDCl_3$ 300 MHz, δ(ppm): 4.23 (s, 2H) 3.79-3.41 (m, 4H) 1.71 (m, 1H) 1.64-1.49 (m, 2H) 0.92 (d, 3H, J=6 Hz) **^{13}C-NMR**; $CDCl_3$ 75 MHz, δ(ppm): 67.77 (t) 60 53 (t) 37.20 (t) 33.77 (d) 17.06 (q); $[\alpha]_D^{20}$ 13.6 (c 3.3, MeOH) lit[6]: $[\alpha]_D^{20}$ 13.6 (c 4.3, MeOH)

2(S)-methyl-1,4-butanediol 4b: Prepared as **4a**; $[\alpha]_D^{20}$ -13.3 (c 3.3, MeOH) lit[4] $[\alpha]_D^{20}$ -13.1 (c 3.3, MeOH)

3(R)4(S)5(S)-3-methyl-4-benzylthio-5-(d-menthyloxy)-butyrolactone 5: To a stirred solution of 1.24 g (10 mmol) benzylmercaptane in 30 ml of THF under a N_2 atmosphere was added at -90°C 6.9 ml of n-Buli (1.5N in hexane, 10.4 mmol). After stirring for 30 min at -90°C, during which period a white suspension was formed, a solution of 2.38 g 5(S)-(d-menthyloxy)-2[5H]-furanone (10 mmol) in 15 ml of THF was added during 15 min. After stirring for 1.5 h at -90°C (a clear solution was formed) 5 ml of MeI was added to the reaction mixture and the reaction temperature was subsequently slowly raised to -45°C (maximum -40°C). At this temperature

the reaction mixture was stirred for 3 h before it was poured into 200 ml saturated aq. NH_4Cl, extracted with ether (3x100 ml) and dried (Na_2SO_4). Evaporation of the solvent was followed by chromatography (SiO_2, CH_2Cl_2/hexane 1/1) after which 3.00 g (0.8 mmol, 80%) of **5** was obtained as a wask. **IR**; neat, cm^{-1}: 1788 C=O **^{1}H-NMR**; $CDCl_3$ 300 MHz, δ (ppm): 7.31-7.21 (m, 5H) 5.45 (d, 1H, J=5.1 Hz) 3.77 (AB, 2H, J=13.9 Hz, ν=26.3 Hz) 3.48 (dt, 1H, J=3.7 Hz, J=10.2 Hz) 2.71 (dd, 1H, J=5.1 Hz, J=9.5 Hz) 2.35 (dq, 1H, J=9.5 Hz, J=7.3 Hz) 2.12-2.04 (m, 2H) 1.66-1.56 (m, 2H) 1.38-1.12 (m, 2H) 1.13 (d, 3H, J=7.3 Hz) 1.05-0.68 (m, 3H) 0.98 (d, 3H, J=6.6 Hz) 0.86 (d, 3H, J=7.3 Hz) 0.72 (d, 3H, J=6.6 Hz) **^{13}C-NMR**; $CDCl_3$ 75 MHz, δ (ppm): 175.40 (s) 137.25 (s) 128.89 (d) 128.49 (d) 127.30 (d) 105.17 (d) 78.47 (d) 50.69 (d) 47.79 (d) 41.35 (d) 39.80 (t) 35.86 (t) 34.18 (t) 31.31 (d) 25.27 (d) 22.98 (t) 22.19 (q) 20.84 (q) 15.62 (q) 13.88 (q) **HRMS**; calcd: 376.207, exp: 376.206; anal calcd for $C_{22}H_{32}O_3S$ C: 70.17, H: 8.57, exp C: 70.06, H: 8.57; $[\alpha]_D^{RT}$ 0.57 (c 2.5, $CHCl_3$)

Warning: We strongly suspect this compound of being a lachrymator therefor it should be handled carefully in a well ventilated hood.

3(S)5(S)-3-methyl-S-(d-menthyloxy)-butyrolactone 6: To a stirred solution of 380 mg **5** (1 mmol) in 25 ml of THF was added 3 teaspoons of Raney Nickel. After stirring for 16 h the solution was decanted and the Raney Nickel was washed 5 times with ether. The combined organic layers were dried (Na_2SO_4) and the solvent evaporated to give 253 mg (1 mmol, 100%)

of the pure adduct as a white solid. This solid was recrystallized from hexane to provide analytically pure **6** mp 103.8-105.9°C. **IR**; KBR, cm^{-1}: 1780 C=O **^{1}H-NMR**; $CDCl_3$ 300 MHz, δ (ppm): 5.66 (dd, 1H, J=4.3 Hz, J=4.9 Hz) 3.53 (dt, 1H, J=4.2 Hz, J=10.8 Hz) 2.69-2.50 (m, 2H) 2.20-2.05 (m, 2H) 1.82-1.72 (m, 1H) 1.69-1.59 (m, 2H) 1.40-1.18 (m, 2H) 1.33 (d, 3H, J=6.7 Hz) 1.08-0.72 (m, 3H) 0.93 (d, 3H, J=6.7 Hz) 0.89 (d, 3H, J=6.7 Hz) 0.80 (d, 3H, J=6.7 Hz) **^{13}C-NMR**; $CDCl_3$ 75 MHz, δ (ppm): 176.69 (s) 99.31 (d) 77.43 (d) 47.67 (d) 39.77 (t) 36.68 (t) 34.52 (d) 34.27 (t) 31.31 (d) 25.36 (d) 22.92 (t) 22.19 (q) 20.90 (q) 16.63 (q) 15.50 (q) **HRMS**; calcd: 254.188, exp: 254.189; anal calcd for $C_{15}H_{26}O_3$ C: 70.83, H: 10.30, exp C: 70.60, H: 10.34; $[\alpha]_D^{RT}$ 176 (c 0.3, hexane)

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(Accepted in The Netherlands 20 December, 1991)